PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2005/000132	19.01.2005	19.01.2004

International Patent Classification (IPC) or both national classification and IPC
C07D239/42

Applicant
RANBAXY LABORATORIES LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☐ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Schuemacher, A Telephone No. +49 89 2399-7818

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IB2005/000132

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language .

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 19

because:

☒ the said international application, or the said claims Nos. 19 for industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	8-15,16
	No:	Claims	1-7, 17-19
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-19
Industrial applicability (IA)	Yes:	Claims	1-18
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 19 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV

Lack of unity of invention

The separate inventions are:

Claims 1-5,8-15,17:

amorphous rosuvastatin magnesium salt and the process for its preparation.

Claims 6,7:

process for the preparation of crystalline rosuvastatin magnesium salt.

Claim 16:

process for the preparation of rosuvastatin calcium salt starting from the amorphous magnesium salt.

Claim 18 and 19:

pharmaceutical composition comprising rosuvastatin magnesium salt and its use as HMG-CoA reductase inhibitor in the treatment of hyperlipidaemia.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

In order to fulfil the requirements of Rule 13.1 PCT, a group of claimed inventions must be so linked as to form a single general inventive concept. The single general inventive concept is only present when each invention possesses the same or corresponding special technical features. These special technical features are those which distinguish the invention from the prior art.

The technical problem addressed by claims 1-15, 8-15 and 17 appears to be the provision of amorphous magnesium salt of a known compound, namely rosuvastatin.

The technical problem addressed by claims 6 and 7 is the provision of a crystalline form of rosuvastatin magnesium salt.

The technical problem addressed by claim 16 is the provision of a calcium salt of rosuvastatin,

whereas the technical problem addressed by claims 18 and 19 is the provision of amorphous rosuvastatin magnesium salt -or the pharmaceutical composition thereof- which can be used as HMG-CoA reductase inhibitor for the treatment of hyperlipidemia.

The common element linking the subject-matter of claims 1-5, 8-15 and 17 with the process of claims 6 and 7 or the process of claim 16 and the medical use claims 18 and 19 is rosuvastatin. However, this compound is already known, as well as its use as HMG-CoA reductase inhibitor in the treatment of hyperlipidemia, from the prior art document EP0521471. Thus, this compound cannot be the special technical feature required by Rule 13.2 PCT.
As neither the technical problems nor the special technical features are the same or corresponding, the requirements of unity are not fulfilled.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 01/60804 A (ASTRAZENECA AB; ASTRAZENECA UK LTD) 23.08.2001
D2: US-B1-6 589 959 (TAYLOR NIGEL P) 8 July 2003
D3: EP-A-0 521 471 (SHIONOGI SEIYAKU KABUSHIKI KAISHA) 7.01.1993
D4: WO03/016317 A (TEVA PHARMA. INDUS. LTD) 27.02.2003

1.

With regard to the prior art disclosed in the documents cited above the subject-matter of the present application, i.e the amorphous magnesium salt of rosuvastatin and the processes for its preparation, does not appear to fulfil the requirements of novelty, cf. Article 33(2) PCT:
D1 anticipated the subject-matter of present claims 6 and 7 as it discloses the preparation of crystalline magnesium salt of rosuvastatin (see example 9). D1 discloses also the preparation of amorphous calcium salt but starting form the methylammonium salt (see example 10).
D2 discloses the preparation of the crystalline calcium salt of rosuvastatin staring from the amorphous calcium form; according to the statement on col. 2, l.11-40, this amorphous form to be used as starting material may be obtained as described in EP-0521471 (D3).
Thus, even if it is not explicitly mentioned, the compounds of D3 are amorphous:
D3 discloses the amorphous sodium and calcium salt of rosuvastatin and since the subject-

matter of claim 1 of D3 encompasses also the pharmaceutic acceptable salt, which according to the description, p.2, l.42-45, can also be the magnesium salt, D3 discloses also the amorphous magnesium salt.
Moreover, the subject-matter of present claims 2-5 is related to the amorphous magnesium salt characterised by a ceratin degree of purity : According to Decision T728/98 (O.J. EPO 2001, 319) and T990/96 (O.J. EPO, 1998, 489), the level of purity of a low molecular compound cannot entail novelty.
Thus, D3 anticipates the subject-matter of present compound-claims 1-5, 17 as well as the pharmaceutical composition containing the amorphous magnesium salt (claim 18) and its use in claim 19.
D4 discloses the process for the preparation of the calcium salt of rosuvastatin but directly from the ester of free acid of rosuvastatin.
None of the prior art documents D1-D4 discloses the processes of present claims 8-15:
-the processes of claims 8-10, 12 and 13 differ from those claimed on account of the dissolution of the crystalline salt in an organic solvent.
-the processes of claims 14 and 15 differ from those claimed on account of the removal of the water by an azeotropic distillation using an organic solvent.
-the process of claim 11 differs from those claimed on account of the milling of the crystalline salt.
The subject-matter of claim 16, i.e the preparation of the calcium salt, is novel over D1-D4 because the calcium salt is obtained specifically from the amorphous magnesium salt.

2.
An inventive step for potentially novel subject-matter (claims 8-15) of the first invention can only be assessed once the following point has been clarified :

In the processes of claims 8-10, 12 and 13, the amorphous magnesium salt is prepared starting from a crystalline form that is dissolved in an organic solvent or in a mixture of organic solvent with water (lactonisation step), whereas in the processes of claims 14 and 15, the crystalline rosuvastatin salt is treated under basic or acidic condition in water and in claim 11 the crystalline rosuvastatin is directly subjected to milling.
These three different group of processes have only as common linking features the crystalline rosuvastatin salt as starting material or the obtained amorphous magnesium salt. Both are already known from the prior art D3.

As already mentioned above under point 1), the three groups of process-claims do neither have the same or corresponding contribution over the prior art.
As there is no special technical features as defined in Rule 13.2 PCT that is shared by the three groups of process-claims, there is also a lack of clarity between these three groups of process-claims.
Hence, at the present stage it should first be made clear which part of the application could serve as a basis for a new and allowable claim.

Considering the assessment of inventive step of the first invention, the following could be noticed: The present application is related to amorphous magnesium salt of rosuvastatin (claims 1-5 and 17) and the processes for its preparation (claims 8-15).
D3 and D1, considered to be the closest prior art documents, disclose the preparation of the amorphous calcium salt (example 10 in D1 and example 7 in D3); additionally, the amorphous non-toxic pharmaceutically acceptable salt, among them the magnesium salt, is disclosed generically in claim 1 of D3.
The technical problem to be solved by the present invention may therefore be formulated as being the provision of an amorphous rosuvastatin magnesium salt, which presents an unexpected effect with regard to the prior art D1 or D3.
However, there is no appropriate information that clarify where an inventive step lies in the invention and which unexpected effect is associated with it since there is no evidence for a surprising effect compared to D1/D3.
The dependent claims do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step (Article 33(3) PCT).

Considering the assessment of inventive step of the third invention (Claim 16):
For the same reason as above, the technical problem to be solved by the present invention may be formulated as being the provision of an improved process for the preparation of the calcium salt of rosuvastatin compared to example 10 in D1, example 1 of D2 or example 7 in D3.
There is no appropriate information that clarify where an inventive step lies in this invention and which unexpected effect is associated with the use of amorphous magnesium salt as starting material instead of the methyl ammonium salt (in D1), the calcium salt (in D2) or the sodium salt (in D3) for the preparation of the calcium salt of rosuvastatin. In the absence of

evidence for an improvement compared to D1-D3, the process of claim 16 cannot be considered to involve an inventive step (Article 33(3) PCT).

Re Item VI

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO2004/014872	19.02.2004	07.08.2003	13.08.2002
WO2004/108691	16.12.2004	03.06.2004	05.06.2004
WO2005/021511	10.03.2005	27.08.2003	

These documents disclose the process for the preparation of magnesium or calcium salt of rosuvastatin.

Re Item VIII

Certain observations on the international application

Although the claims 1-5, 8-15 and 17 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.

Claim 17 contains a reference to the drawings. According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here, because the X-Ray diffraction pattern of an amorphous compound is so broad that it seems not appropriate to define a compound.